CANCER FACTS
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# Menopausal Hormone Replacement Therapy

## Menopause

Menopause is the time in a woman's life when hormonal changes cause menstruation to stop permanently. For most women, menopause is the last stage of a gradual biological process that actually begins during their mid-thirties.

Menopause is considered complete when a woman has stopped menstruating, or having her period, for 1 year. This usually occurs between ages 45 and 55, with variations in timing from woman to woman. By the time natural menopause is complete, hormone output has decreased significantly, but does not completely stop. Women who have surgery to remove their uterus (an operation called a hysterectomy) and/or both of their ovaries (an operation called bilateral oophorectomy) experience "surgical menopause," the immediate cessation of ovarian hormone production and menstruation. Doctors may recommend hormone replacement therapy (HRT), using either estrogen alone (usually in women who have had a hysterectomy) or estrogen in combination with progestin (a form of progesterone) to counter some of the possible effects of natural or surgical menopause on a woman's health and quality of life.

Because of advances in medical care and fewer deaths during childbirth, the average life expectancy for women in the United States increased from 51 years in 1900 to 79 years in 2000. A 50-year-old woman today can expect to live at least one-third of her life after menopause. An estimated 40 million women will go through menopause in the next 20 years. Thus, an increasing number of women will need to weigh the benefits and risks of HRT.

Although menopause is defined by many people as simply the end of a woman's menstrual cycles and her ability to bear children, it is also the beginning of a new and distinct phase of her life, with its own special health issues.

**Symptoms of Menopause**

Each woman experiences menopause differently. Some women have minimal discomfort, while others have moderate or even severe problems. Hot flashes, the most common symptom, occur in more than 60 percent of menopausal women. Hot flashes often begin several years before other symptoms of menopause occur.

Other changes involve the vagina and urinary tract. Declining estrogen levels can make vaginal tissue drier, thinner, and less elastic, which can make sexual intercourse painful. Urinary tract tissue also becomes less elastic, sometimes leading to involuntary loss of urine upon coughing, laughing, sneezing, exercising, or sudden exertion (stress incontinence). Urinary tract infections tend to occur more frequently. Other possible effects of menopause include sleep disturbances and mood swings.

## Health Effects of Menopause

In addition to producing some potentially uncomfortable symptoms, menopause can have more serious, long-term effects on a woman's overall health and potential years of life. For example, the drop in estrogen that occurs at menopause is thought to cause adverse changes in levels of cholesterol and other blood lipids (fats), and in levels of fibrinogen (a substance that affects blood clotting). These changes may increase the risk of heart disease (the leading cause of death among American women) and stroke. More than 370,000 women in this country die each year from heart disease, and about 93,000 die from stroke.

Osteoporosis (thinning and weakening of the bones), another serious concern during later life, is aggravated by menopause. Menopause speeds up the bone mineral depletion that occurs during normal aging processes and increases the risk of fractures. About 20 percent of women over age 50, or about 8 million American women, have or are at risk for bone fragility and fractures as their estrogen levels decline. Fractures, especially hip fractures, often require a long recovery period and are a common injury in women with osteoporosis. Fractures of the vertebrae can cause curvature of the spine (also called kyphosis), loss of height, and pain.

## Hormone Replacement Therapy

Most women will eventually need to make decisions about whether to take HRT and, if so, for how long. Hormone replacement therapy can have beneficial effects, but there are also some concerns associated with it. Each woman should consider both risks and benefits when making her decisions.

*Benefits of HRT*

It has been well documented for several decades that HRT is the most effective remedy for the hot flashes and sleep disturbances that often accompany menopause. Hormone replacement therapy has also consistently been shown to decrease vaginal discomfort by increasing the thickness, elasticity, and lubricating ability of vaginal tissue. Urinary tract tissue also becomes thicker and more elastic, which may reduce the incidence of stress incontinence and urinary tract infections.

Although HRT was used initially to reduce the discomfort from short-term menopausal symptoms, studies have provided evidence that it may prevent or reduce some of the negative long-term health effects of menopause. Scientists continue to gather information to define the potential benefits from HRT and to identify the women for whom it may be most useful. Further research is also needed to determine when HRT should be started and how long it should be continued to achieve the greatest benefits.

Hormone replacement therapy plays a significant role in maintaining bone density, thus helping to prevent osteoporosis. HRT is also used to treat bone loss that has already begun. HRT can prevent the decline of bone density and may reduce the incidence of fractures. It has been shown, however, that bone loss resumes upon discontinuation of HRT.

Research shows that HRT improves the levels of some blood lipids and lowers fibrinogen levels. Some studies suggest that HRT may reduce the risk of heart disease and stroke. However, scientists are concerned that some of the apparent benefits of HRT in these studies may be due to the fact that healthier or more health-conscious women may be more likely to take replacement hormones. Well-designed, placebo-controlled studies of postmenopausal women with heart disease found that the use of HRT did not prevent further heart attacks or

death from heart disease. Other studies showed that HRT may initially increase the risk of heart attacks, but the risk levels out over time. Additional research is in progress to clarify this issue.

Some, but not all, studies suggest that taking estrogen may reduce the risk of developing Alzheimer's disease. However, scientists caution that additional research is needed to explore this possibility.

*Concerns About HRT*

Although HRT has potential benefits for many menopausal and postmenopausal women, it can also have drawbacks. Concerns about HRT center on the risk of endometrial cancer, ovarian cancer, and breast cancer, especially after long-term use (more than 10 years).

Endometrial Cancer (Cancer of the Uterus)

When estrogen replacement became available for menopausal women in the 1940s, it was administered in high doses without progestin. As it became more popular in the 1960s, it was given to increasing numbers of women. In the 1970s, however, it became clear that women who received estrogen alone had a six- to eightfold increased risk of developing cancer of the endometrium (lining of the uterus).

Now, most doctors prescribe HRT that includes progestin, along with much lower doses of estrogen than were used initially, for women who have *not* had a hysterectomy. Progestin counteracts estrogen's negative effect on the uterus by preventing the overgrowth of the endometrial lining. Adding progestin to HRT substantially reduces the increased risk of endometrial cancer associated with taking estrogen alone. (A woman who has had a hysterectomy does not need progestin and can receive HRT with estrogen alone.)

Because reports have shown that estrogen increases the risk of developing endometrial cancer, many women and their doctors are also concerned that HRT may increase the risk of recurrence in women with a history of endometrial cancer. At present, however, there is no scientific evidence that taking estrogen increases this risk. To help resolve this issue, the National Cancer Institute (NCI) is sponsoring a clinical trial to determine the effects of estrogen in women treated for early stage endometrial cancer. The study will compare recurrence rates between women who are given estrogen and those who are not given estrogen.

Ovarian Cancer

The results of past studies have not shown a clear link between HRT and the risk of ovarian cancer. However, recently reported data from two large, long-term studies have suggested that there may be an association between the use of HRT after menopause and an increased risk of ovarian cancer.

A study conducted by the American Cancer Society followed 211,581 postmenopausal women who had no history of cancer at the time of enrollment. Results of followup from 1982 through 1996 showed that women who used HRT for 10 or more years had an increased risk of dying from ovarian cancer, compared with women who had never used HRT or had used it for less than 10 years. Information on the type of HRT the participants used (such as estrogen-only or estrogen plus progestin) was not available. However, the majority of women using HRT at the beginning of the study probably used estrogen-only HRT.

Research conducted by the NCI as part of its Breast Cancer Detection Demonstration Project (BCDDP) Followup Study also examined the risk of ovarian cancer in postmenopausal women using HRT. The study followed 40,762 postmenopausal, cancer-free women from 1979 through 1998. The results suggested that estrogen-only HRT is associated with an increased risk

of ovarian cancer when compared with HRT that includes progestin. More research is needed to clarify the relationship between HRT and the risk of ovarian cancer in postmenopausal women.

Breast Cancer

The relationship between HRT and breast cancer has not yet been completely clarified. The possible increased risk of developing breast cancer is consistently cited by menopausal and postmenopausal women as the main reason they are reluctant to use HRT. Many women and their doctors have particular concerns about the effects of long-term HRT use on breast cancer risk.

One of the most important risk factors for developing breast cancer is a woman's lifelong exposure to naturally occurring reproductive hormones, such as estrogen, because the longer her body produces these hormones, the more likely she is to develop breast cancer. Factors such as early menstruation (before age 12) and late menopause (after age 55) contribute to prolonged hormone exposure. Because of this relationship between prolonged hormone exposure and breast cancer risk, scientists have been concerned that increasing a woman's lifelong exposure to hormones with HRT would result in increased breast cancer risk.

Over the last 25 years, numerous observational studies have examined the possible relationship between HRT and breast cancer. These studies have varied widely in terms of study design; size of populations studied; and doses, timing, and types of hormones used. Results of these studies have been inconsistent. Some of the early studies that followed women who used estrogen-only HRT for long periods of time showed increased breast cancer risk. Other studies have looked at the experience of women who took estrogen combined with progestin. Some have shown an increased risk, while others have not.

A large study conducted by the Collaborative Group on Hormonal Factors in Breast Cancer showed an increased risk of developing breast cancer among current or recent HRT users. The researchers analyzed data from 51 studies on over 52,000 women with breast cancer and over 108,000 women without breast cancer. Their analysis indicated that the risk of developing breast cancer increases with the length of HRT use, but decreases after a woman stops taking HRT. They also found that, 5 years after discontinuing HRT, the elevation in a woman's risk of breast cancer had almost disappeared. Most of the women included in the study used estrogen-only HRT. The relationship of breast cancer risk and HRT that contains both estrogen and progestin is less certain; several other studies have focused on this relationship. Some have shown an increased risk, while others have not.

Two studies compared the risk of breast cancer for women who had taken estrogen-only HRT with the risk for women who had taken HRT using estrogen combined with progestin. The first study analyzed data on 46,000 women. The researchers found that the risk for breast cancer among women who had used HRT during the past 4 years was higher than the risk for women who did not use HRT. For women who had taken the combination HRT, the risk of breast cancer was 8 percent higher per year of HRT use. For women who had taken the estrogen-only therapy, the risk of breast cancer was 1 percent higher per year of HRT use. There was no increase in risk among women who had stopped using either type of HRT at least 4 years prior to the study.

The second study focused on nearly 1,900 postmenopausal women diagnosed with breast cancer and more than 1,600 controls matched for age, race, and neighborhood. The researchers found that, for combined HRT, the risk of developing breast cancer increased by 24 percent for every 5 years of use; for estrogen-only therapy, the risk increased by 6 percent every 5 years.

Both studies reported that the increased risk of breast cancer associated with either type of HRT was more pronounced in thin women. More research is needed to test the effects of lower doses of HRT on the symptoms of menopause and breast cancer risk in thin women.

The results of these studies indicate that HRT containing both estrogen and progestin may have different effects on breast tissue than it does on ovarian tissue. Whereas combination HRT may be associated with a lower risk of ovarian cancer when compared with estrogen-only HRT, the opposite appears to be true for breast cancer risk.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was designed to study the effects of different HRT regimens in postmenopausal women. Data from the trial indicate that about 25 percent of women who use HRT that includes a combination of progestin and estrogen have an increase in breast density on their mammograms. In the PEPI study, about 8 percent of women taking estrogen-only HRT also had increased breast density. Increased density is a concern because other studies have shown that women age 45 and older whose mammograms show at least 75 percent dense tissue are at increased risk for breast cancer. However, researchers do not know if increased breast density due to HRT carries the same risk for breast cancer as having naturally dense breasts.

Increased breast density from HRT makes it more difficult for a radiologist to read some mammograms, sometimes leading to the need for followup mammograms and breast biopsies. One study showed that stopping HRT for about 2 weeks before having a mammogram improved the readability of the mammogram. However, further research is needed to confirm the usefulness of this approach.

There is also considerable uncertainty about the relationship between a woman's risk of developing breast cancer and the length of time she receives HRT. Some women take HRT for

only a few years, until the worst of their menopausal symptoms have passed, while others take it for a decade or more. Some researchers believe that there is little or no increased risk of breast cancer associated with short-term use (3 years or less) of either HRT with estrogen alone or estrogen combined with progestin, while long-term use is linked to an increased risk.

Still another area of controversy centers on whether women who have had breast cancer can take HRT, especially since treatments for breast cancer can often lead to early menopause in younger women. Use of HRT in breast cancer survivors is widely discouraged because of the concern that exposure to the estrogen in HRT would increase their risk for recurrence. However, the prognosis of women who took HRT before developing breast cancer seems to be better than that of women who did not do so. It is uncertain whether this finding is a result of increased doctor visits leading to earlier detection or is due to the HRT. Women with a history of breast cancer should talk with their doctor about HRT so that they can make an informed decision.

**Botanical Treatments**

Some women who are concerned about conventional HRT have turned to nonprescription remedies, such as phytoestrogens or other botanical products, to relieve their menopausal symptoms. Phytoestrogens are weak estrogen-like substances that are found in foods such as soy products, whole-grain cereals, seeds, and certain fruits and vegetables. Phytoestrogens can also be obtained in the form of soy tablets. Some women have also tried other botanical treatments, including herbs and certain food products (such as wild or Mexican yams), to relieve the symptoms of menopause.

The American College of Obstetricians and Gynecologists (ACOG) suggests that short-term use of the phytoestrogens in soy may be helpful for relieving hot flashes and night

sweats. Although soy is safe in dietary amounts, the ACOG found that large amounts of soy supplements may be harmful to women, particularly women with a history of estrogen-dependent cancer. Researchers are also studying whether phytoestrogens affect a woman's risk of cancer.

Although some herbal remedies may help relieve menopausal symptoms, others have been shown to be ineffective. In addition, because many botanical products are not regulated, a product's content, quality, and efficacy may be uncertain. More research is needed to determine the safety and effectiveness of herbal treatments, and to find out about any dangerous interactions that these treatments may have with other drugs a woman is taking. To make an informed decision about the use of phytoestrogens, other botanical treatments, and HRT, women should talk with their doctor.

**The Future of HRT**

In an effort to find definitive answers, the Women's Health Initiative (WHI) and other carefully designed studies are evaluating the effects of long-term use of HRT in postmenopausal women. Sponsored by the National Institutes of Health, the WHI is a 15-year nationwide clinical trial that is investigating heart disease, osteoporosis, and breast and colon cancers in 63,000 women ages 50 to 79. Long-term, well-designed studies such as the WHI should be able to answer many of the lingering questions about the true effects of HRT.

Weighing benefits and risks is part of all medical decisions. Some women and their doctors feel that HRT's potential beneficial effects on cardiovascular disease, osteoporosis, and general quality of life outweigh the risk of developing cancer. Others are concerned about the possible negative effects of long-term HRT use. Many women choose to reduce the risks of

osteoporosis and heart disease by exercising regularly, avoiding tobacco products, eating a balanced diet, and/or taking calcium, vitamin D, or other medications.

Ultimately, physicians emphasize that each woman's decision about whether to take HRT and, if so, for how long, must be an individual one made in cooperation with her physician. This decision should be based on the woman's individual risk profile—her personal and family medical history, not only of cancer, but also of heart disease, stroke, and osteoporosis.

**Resources**

The following Federal Government agencies can provide information related to hormone replacement therapy:

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| **Organization:** | **National Institute on Aging (NIA)**<br>**Public Information Office** |
| Address: | Building 31, Room 5C27<br>31 Center Drive, MSC 2292<br>Bethesda, MD 20892 |
| Telephone: | 301–496–1752<br>1–800–222–2225 |
| TTY: | 1–800–222–4225 (for deaf and hard of hearing callers) |
| Internet Web site: | http://www.nih.gov/nia/ |

The NIA Public Information Office offers printed material about hormone therapy and the management of symptoms and issues related to menopause, and the prevention of chronic diseases of aging including osteoporosis, heart disease, and stroke.

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| **Organization:** | **National Institutes of Health (NIH)**<br>**Osteoporosis and Related Bone Diseases–National Resource Center** |
| Address: | 1232 22nd Street, NW.<br>Washington, DC 20037–1292 |
| Telephone: | 202–223–0344<br>1–800–624–BONE (1–800–624–2663) |
| TTY: | 202–466–4315 (for deaf and hard of hearing callers) |
| Fax: | 202–293–2356 |
| Internet Web site: | http://www.osteo.org |

The NIH Osteoporosis and Related Bone Diseases National Resource Center distributes printed material about osteoporosis prevention and treatment.

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| **Organization:** | **National Heart, Lung, and Blood Institute (NHLBI) Information Center** |
| Address: | Post Office Box 30105<br>Bethesda, MD 20824–0105 |
| Telephone: | 301–592–8573 |
| Fax: | 301–592–8563 |
| Internet Web site: | http://www.nhlbi.nih.gov/index.htm |

The NHLBI Information Center provides printed material about heart disease and its risk factors.

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| **Organization:** | **National Institute of Neurological Disorders and Stroke (NINDS)** |
| Address: | Post Office Box 5801<br>Bethesda, MD 20824 |
| Telephone: | 1–800–352–9294 |
| Internet Web site: | http://www.ninds.nih.gov |

The NINDS Office of Communications and Public Liaison distributes printed material about stroke and other neurological disorders.

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| **Organization:** | **Women's Health Initiative (WHI) Program Office** |
| Address: | Suite 300 MS 7966<br>One Rockledge Centre<br>6705 Rockledge Drive<br>Bethesda, MD 20892–7966 |
| Telephone: | 301–402–2900 |
| Fax: | 301–480–5158 |
| Internet Web site: | http://www.nhlbi.nih.gov/whi/ |

The WHI Program Office provides information about the WHI.

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## Sources of National Cancer Institute Information

**Cancer Information Service**

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

**NCI Online**

***Internet***

Use http://cancer.gov to reach NCI's Web site.

***CancerMail Service***

To obtain a contents list, send e-mail to cancermail@cips.nci.nih.gov with the word "help" in the body of the message.

**CancerFax®** fax on demand service

Dial 1–800–624–2511 or 301–402–5874 and follow the voice-prompt instructions.

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